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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/586,242	06/02/2000	James McKim	28341/6281A	6518

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EXAMINER	
WITZ, JEAN C	

ART UNIT	PAPER NUMBER
1651	7

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/586,242	MCKIM ET AL.	
	Examiner	Art Unit	
	Jean C. Witz	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *12-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,21-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 16 is acknowledged. The traversal is on the ground(s) that that the inventions are not independent and distinct. This argument has been found persuasive. The restriction requirement between Group I and Group II is withdrawn. Applicants' election of glutathione S-transferase, ATP assay, cell number count, MTT assay and alamar blue as the first, second, third, fourth and fifth indicator of cell health. Claims 12-19 are withdrawn from consideration as the species elected as the first indicator falls with the membrane integrity group, the second falls in the mitochondrial function group and the third falls within the cell mortality group. This elected grouping of tests is distinct from the grouping set forth in claim 12.

Claim Rejections - 35 USC § 112

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 requires that the plurality of concentrations include at least two concentrations above the Ctox concentration; however, the concentrations are selected prior to the selection of the Ctox concentration. It remains unclear, and therefore vague and indefinite, as to how the Ctox may be known before its selection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11 and 20-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Yao et al., Chung et al., Garza-Ocanas et al., and Morrison et al.

The claims are drawn to a toxicity screening methods where at least three cytotoxicity assays are performed so as to evaluate the toxicity of a test compound. Various concentrations of the test compound are used, controls are used. Other methods that are related to the use of cytotoxicity assays are claimed.

Yao et al. evaluates the irritancy potential of chemicals by culturing rabbit conjuctival epithelial cells. Injury to these cells by surfactants at various concentrations was assessed by lactate dehydrogenase assay, a neutral red assay, and an MTT assay. EC50 values were calculated for each indicator. In vivo toxicity as evidenced by the Draize test was seen to correlate to the in vitro results.

Chung et al. evaluates the cytotoxicity of adriamycin, using a neutral red assay, an MTT assay, and LDH assay and a protein content assay. Controls are used for comparison and multiple concentrations of adriamycin are tested.

Morrison et al. evaluates the biocompatibility of two polymers that may be used in orthopedic implants by doing a cell protein assay, a GSH assay, a LDH assay, and an MTT assay on osteoblasts exposed to the polymers.

Finally, Garza-Ocanas et al. assessed and compared the in vitro toxicity of two buckthorn toxins on cultures of hepatocytes and keratinocytes. Cytotoxicity was measured by LDH assay, MTT assay and neutral red assay. Multiple concentrations of toxins were tested.

The prior art indicates that it is conventional to use multiple tests to evaluate the cytotoxicity of a test compound. It is also conventional to use multiple concentrations within those claimed. The use of controls is also conventional. Creating graphs of data is also deemed conventional. It would have been obvious to one of ordinary skill in the art at the time the invention was made to select at least three conventional cytotoxicity tests, to use multiple concentrations, to use a control and to graph the results. The claims recite the selection of two values: the Ctox and the TC50. The TC50 is

equivalent to other conventional evaluative values, the EC50 and the LD50, such that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a 50% level as a determinative value of the toxicity of a compound. Ctox is defined as the concentration of the test compound that is the highest amount of the test compound that shows no observable toxic effect in all tests performed. Since each test measures the toxicity of the test compound differently, it would have been illogical to pick a concentration that may have little effect on membrane integrity but shows toxicity in mitochondrial function. Determination of an across-the-board lack of toxicity of a specific concentration would have been obvious to one of ordinary skill in the art.

Finally, all of the other methods are permutations of conventional uses of standard cytotoxicity tests. Toxicity tests are conventionally performed when one of ordinary skill in the art is developing an agent for treatment of a disease or disorder, is identifying a lead compound for drug development, is screening chemical compounds to select candidate therapeutic agents, is prioritizing candidate therapeutic agents for pharmaceutical research and is predicting in vivo toxicity of chemical compounds. Therefore, if it would have been obvious to use the toxicity evaluation method such as claimed, it would have been similarly prima facie obvious to engage in the other methods such as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jean C. Witz whose telephone number is (703) 308-3073. The examiner can normally be reached on 6:30 a.m. to 4:00 p.m. M-Th and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jean C. Witz
Primary Examiner
Art Unit 1651

August 11, 2003